Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Cryptococcosis (Last updated May 7, 2013; last reviewed May 7, 2013)

Epidemiology

Most HIV-associated cryptococcal infections are caused by *Cryptococcus neoformans*, but occasionally *Cryptococcus gattii* is recognized. *C. neoformans* is found worldwide, whereas *C. gattii* most often is found in Australia and similar subtropical regions and in the Pacific Northwest. Before the era of effective antiretroviral therapy (ART), approximately 5% to 8% of HIV-infected patients in developed countries were diagnosed with disseminated cryptococcosis.[1] Current estimates indicate that every year, nearly 1 million cases of cryptococcal meningitis are diagnosed worldwide and the disease accounts for more than 600,000 deaths.[2] In the last decade, incidence has declined substantially in areas with access to effective ART, and most new infections are being recognized in patients recently diagnosed with HIV infection.[3] Most cases are observed in patients who have CD4 T-lymphocyte (CD4) cell counts <100 cells/mm^{3}.

Clinical Manifestations

In HIV-infected patients, cryptococcosis commonly presents as a subacute meningitis or meningoencephalitis with fever, malaise, and headache.[1] Classic meningeal symptoms and signs, such as neck stiffness and photophobia, occur in only one-quarter to one-third of patients. Some patients experience encephalopathic symptoms, such as lethargy, altered mentation, personality changes, and memory loss that are usually a result of increased intracranial pressure, thought to result from impaired cerebrospinal fluid (CSF) absorption, or yeast infection of the brain.

Cryptococcosis usually is disseminated when diagnosed in an HIV-infected patient. Any organ of the body can be involved, and skin lesions may be myriad, including umbilicated skin lesions mimicking molluscum contagiosum. Isolated pulmonary infection is also possible; symptoms and signs include cough and dyspnea in association with an abnormal chest radiograph, which typically demonstrates lobar consolidation, although lobar and nodular infiltrates have been reported. Pulmonary cryptococcosis may present as acute respiratory distress syndrome and mimic *Pneumocystis* pneumonia.

Diagnosis

Analysis of CSF generally demonstrates mildly elevated levels of serum protein, low-to-normal glucose concentrations, and pleocytosis consisting mostly of lymphocytes. Some HIV-infected patients will have very few CSF inflammatory cells, but an India ink or Gram's stain preparation often will demonstrate numerous yeast forms. The opening pressure in the CSF may be elevated, with pressures ≥25 cm H_2O occurring in 60 to 80% of patients.[4,5]

Cryptococcal disease can be diagnosed through culture of blood or CSF, CSF microscopy with India ink staining, or cryptococcal antigen (CrAg) detection. In patients with HIV-related cryptococcal meningitis, 55% of blood cultures and 95% of CSF cultures are positive and visible colonies can be detected within 7 days. India ink staining of CSF demonstrates encapsulated yeast in 60% to 80% of cases, but many laboratories in the United States no longer perform this test. CSF CrAg is usually positive in patients with meningoencephalitis. Serum CrAg is usually positive in both meningeal and non-meningeal infection and may be present weeks to months before symptom onset.[6] A positive serum CrAg should prompt a lumbar puncture to rule out meningeal disease. Three methods exist for antigen detection: latex agglutination, enzyme immunoassays, and lateral flow assay (a newly developed dipstick test). Testing for the antigen is a useful initial screening tool in diagnosing cryptococcosis in HIV-infected patients,[7] and it may be particularly useful when lumbar punctures need to be delayed or are refused.

Preventing Exposure

Cryptococcus is ubiquitous in the environment; it is found in soils. HIV-infected patients cannot completely avoid exposure to *C. neoformans* or *C. gattii*. Limited epidemiological evidence suggests that exposure to aged bird droppings may increase risk of infection.

Preventing Disease

Because the incidence of cryptococcal disease is low among HIV-infected patients in the United States, routine testing of asymptomatic persons for serum cryptococcal polysaccharide antigen is not recommended for patients residing there.

Prospective, controlled trials indicate that prophylactic fluconazole or itraconazole can reduce the frequency of primary cryptococcal disease in patients who have CD4 cell counts <100 cells/mm^3.[8,9] However, in the United States, primary prophylaxis or screening for serum CrAg in asymptomatic patients is not recommended because of the relative infrequency of cryptococcal disease, lack of survival benefit associated with prophylaxis, possibility of drug interactions, potential antifungal drug resistance, and cost **(BII)**.

Treating Disease

Treating cryptococcosis consists of three phases: induction, consolidation, and maintenance therapy. The preferred induction treatment for cryptococcal meningitis and other forms of extrapulmonary cryptococcosis is a lipid formulation of amphotericin B in combination with flucytosine **(AI)**. Historically, amphotericin B deoxycholate was the preferred formulation at a dose of 0.7 to 1.0 mg/kg daily **(AI)**. However, based on the growing body of evidence that lipid formulations of amphotericin B are effective for disseminated cryptococcosis and should be used as the preferred formulation **(AI)**, particularly in patients who experience clinically significant renal dysfunction during therapy or who are likely to develop it. The non-comparative CLEAR study demonstrated a 58% response rate in HIV-infected patients treated with amphotericin B lipid complex at mean dose of 4.4 mg/kg daily.[10] In a Dutch and Australian study, a 3-week course of liposomal amphotericin B (4 mg/kg daily) resulted in more rapid sterilization of CSF than amphotericin B deoxycholate (0.7 mg/kg daily).[11] A recently published comparison of amphotericin B deoxycholate (0.7 mg/kg daily), and liposomal amphotericin B (AmBisome®) (3 mg/kg or 6 mg/kg daily) showed similar efficacy for the three regimens, but nephrotoxicity was lower with 3 mg/kg daily liposomal amphotericin B.[12]

Therefore, liposomal amphotericin B, in a dose of 3 to 4 mg/kg/daily, is recommended as the preferred amphotericin B formulation for primary induction therapy **(AI)**, based on clinical experience and reduced renal toxicity compared to amphotericin B deoxycholate. Amphotericin B lipid complex in a dose of 5 mg/kg daily is an alternative **(BII)**.

Amphotericin B formulations should be combined with flucytosine at a dose of 100 mg/kg daily in 4 divided doses for ≥2 weeks in patients with normal renal function and is the preferred regimen for primary induction therapy **(AI)**. Renal function should be monitored closely and the flucytosine dose adjusted accordingly for patients with renal impairment. The addition of flucytosine to amphotericin B during acute treatment is associated with more rapid sterilization of CSF.[13-16] A recent randomized clinical trial also showed that the combination of amphotericin B deoxycholate in a dose of 1.0 mg/kg/d combined with flucytosine was associated with improved survival compared to the same dose of amphotericin B without flucytosine.[17]

Amphotericin B deoxycholate in combination with fluconazole 400 mg daily was inferior to amphotericin B in combination with flucytosine for clearing *Cryptococcus* from CSF.[18] However, in two randomized trials, amphotericin B plus fluconazole 800 mg daily compared favorably with amphotericin B alone.[17,19] Therefore, amphotericin B deoxycholate or lipid-formulated amphotericin B alone or combined with fluconazole at 800 mg daily may be viable options in some circumstances but are less preferable alternatives than lipid-formulated amphotericin B combined with flucytosine **(BI)**.

Fluconazole (400–800 mg daily) combined with flucytosine is also a potential alternative to amphotericin B regimens **(BII)**.[20] Fluconazole alone, based on early fungicidal activity, is inferior to amphotericin B[21] for induction therapy and is recommended only for patients who cannot tolerate or do not respond to standard treatment. If it is used for primary induction therapy, the starting daily dose should be 1200 mg **(CII)**.[22]

After at least 2 weeks of successful induction therapy—defined as substantial clinical improvement and a negative CSF culture after repeat lumbar puncture—amphotericin B and flucytosine can be discontinued and follow-up or consolidation therapy initiated with fluconazole 400 mg daily **(AI)**. This therapy should continue for at least 8 weeks **(AI)**.[13,14,23] Subsequently, the fluconazole should be reduced to 200 mg daily and continued as chronic maintenance therapy to complete at least one year of azole therapy (see Preventing Recurrence section below).[24] Limited data are available for the newer triazoles, voriconazole and posaconazole, as either primary or maintenance therapy for patients with cryptococcosis. Most of the data on use of these extended-spectrum triazole antifungals have been reported for treatment of refractory cases, with success rates of approximately 50%.[25,26] At this time, the role of posaconazole and voriconazole in the management of cryptococcosis is not established. Voriconazole should be used cautiously with HIV protease inhibitors and efavirenz.

Non-central-nervous-system (CNS), extrapulmonary cryptococcosis and diffuse pulmonary disease should be treated similarly to CNS disease **(BIII)**. For mild-to-moderate symptoms and focal pulmonary infiltrates, treatment with fluconazole (400 mg daily for 12 months) combined with effective ART is appropriate **(BIII)**. All patients should have their CSF sampled to rule out CNS disease.

Special Considerations with Regard to Starting ART

Optimal timing for initiation of ART in patients with acute cryptococcal meningitis is controversial. One randomized, controlled trial that included 35 patients with cryptococcal meningitis suggested that ART was safe when started within the first 14 days of diagnosis.[27] A subsequent study from Africa demonstrated significantly worse outcomes in 54 patients started on ART within 72 hours of cryptococcal meningitis diagnosis compared with those in which ART was delayed for at least 10 weeks.[28] However, in the latter study, cryptococcal meningitis was managed with fluconazole alone, and ART consisted of nevirapine, stavudine, and lamivudine. Neither fluconazole alone nor the latter ART regimen are recommended as preferred initial treatment in the United States. Lastly, another randomized clinical trial conducted in Africa in hospitalized patients with acute cryptococcal meningitis was recently halted by a Data and Safety Monitoring Board due to higher mortality in the early ART arm (defined as ART started during the hospitalization) compared to the arm in which patients waited to start ART until after their discharge from the hospital. In contrast to the other African study, this study used amphotericin B plus fluconazole during the induction phase of antifungal treatment (http://www.niaid.nih.gov/news/newsreleases/2012/Pages/COAT.aspx). Such data must be viewed with caution until fully reported and analyzed.

In patients with severe cryptococcosis (particularly those with elevated increased intracranial pressure [ICP]), it may be prudent to delay initiation of ART until induction (the first 2 weeks) or the total induction/consolidation phase (10 weeks) has been completed. However, for patients with advanced immunosuppression (CD4 count <50 cells/mm^3) earlier initiation of ART may be necessary **(BIII)**. If the treating physician elects to begin effective ART earlier, preparations should be made to aggressively address complications of immune reconstitution inflammatory syndrome (IRIS) such as elevated ICP **(BIII)**.

All the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain antiretroviral agents. Table 5 lists these interactions and recommendations for dosage adjustments, where feasible.

Monitoring of Response to Therapy and Adverse Events (including IRIS)

ICP can cause clinical deterioration despite a microbiologic response and is more likely if the CSF opening lumbar pressure is ≥25cm H_2O[4,13] when obtained in the lateral decubitus position with good manometrics

assured. In one large clinical trial, increased ICP was associated with 93% of deaths during the first 2 weeks of therapy and 40% of deaths during weeks 3 to 10.[4] Although it is uncertain which patients with high opening lumbar pressures will deteriorate, those with symptoms and signs of ICP require immediate clinical intervention.

Lumbar opening pressure should be measured in all patients with cryptococcal meningitis at the time of diagnosis. Measures to decrease ICP should be used for all patients with confusion, blurred vision, papilledema, lower extremity clonus, or other neurologic signs of increased pressure. Lumbar punctures usually are recommended for initial management. One approach is to remove a volume of CSF (typically 20–30 mL) that at least halves the opening pressure[29] and repeat daily until symptoms and signs consistently improve. CSF shunting through a lumbar drain or ventriculostomy should be considered for patients who cannot tolerate lumbar puncture or in whom signs and symptoms of cerebral edema persist after multiple lumbar taps **(BIII)**. Corticosteroids and mannitol have been shown to be ineffective in managing ICP and **are not recommended (CIII)**. Acetazolamide is hazardous as therapy for increased ICP management in those without signs IRIS and **is not recommended (BII)**.

After the first 2 weeks of treatment, many experts would advocate a repeat lumbar puncture to ensure that viable organisms have been cleared from the CSF. Even in patients who have clinical improvement, positive CSF cultures after 2 weeks of therapy are predictive of future relapse and less favorable outcome. In such cases, some experts would continue amphotericin B plus flucytosine until the CSF cultures are negative **(BIII)**. Monitoring titers of cryptococcal polysaccharide antigen in serum or CSF is of no value in determining response to therapy and **is not recommended**. If new symptoms or clinical findings occur later, a repeat lumbar puncture, with measurement of opening lumbar pressure and CSF culture, should be performed.

Patients treated with amphotericin B formulations should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances. Pre-infusion administration of 500 to 1000 mL of normal saline appears to reduce the risk of nephrotoxicity during amphotericin B treatment. Thirty minutes before infusion, acetaminophen (650 mg) and diphenhydramine (25–50 mg) or hydrocortisone (50–100 mg) typically are administered in an attempt to ameliorate infusion-related adverse reactions **(BIII)**, but data supporting these practices are scant. Meperidine (25–50 mg titrated during infusion) is effective for preventing and treating amphotericin B-associated rigors **(BII)**.

In patients receiving flucytosine, dosage should be adjusted based on changes in creatinine clearance and might be guided by flucytosine levels. Peak serum flucytosine levels should be obtained 2 hours after an oral dose and the therapeutic range is between 30 and 80 µg/mL. Alternatively, frequent (i.e., at least bi-weekly) blood counts can be performed to detect development of cytopenia. Patients treated with flucytosine also should be monitored for hepatotoxicity and gastrointestinal toxicities.

An estimated 30% of HIV-infected patients with cryptococcal meningitis experience IRIS after initiation or reinitiation of effective ART.[30,31] Patients who have cryptococcal IRIS are more likely to be antiretroviral naive, have higher HIV RNA levels, and have less CSF inflammation on initial presentation.[32] Distinguishing IRIS from treatment failure may be difficult. In general, cryptococcal IRIS presents with worsening clinical disease despite microbiological evidence of effective antifungal therapy,[32,33] whereas treatment failure is associated with continued positive cultures. Appropriate management of IRIS is to continue both ART and antifungal therapy and reduce elevated ICP, if present **(AII)**. In patients with severe symptoms of IRIS, some specialists recommend a brief course of glucocorticosteroids **(CIII)**, but data based management strategies have not been developed.

Managing Treatment Failure

Treatment failure is defined as lack of clinical improvement after 2 weeks of appropriate therapy, including management of increased ICP, with continued positive cultures; or relapse after an initial clinical response, defined as recurrence of symptoms with a positive CSF culture after ≥4 weeks of treatment. Direct primary fluconazole resistance with *C. neoformans* has been reported in the United States but is uncommon.[34] Therefore, susceptibility testing is not routinely recommended for intial management of cryptococcosis.

Isolates collected to evaluate for persistence or relapse should, however, be checked for susceptibility and compared with the original isolate. Strains with fluconazole minimum inhibitory concentrations ≥16 µg/mL are considered fluconazole resistant.[35]

Optimal therapy for patients with treatment failure has not been established. Patients who fail to respond to induction with fluconazole monotherapy should be switched to amphotericin B, with or without flucytosine, and remain on it until a clinical response occurs. Liposomal amphotericin B (4–6 mg/kg/day) or amphotericin B lipid complex (5 mg/kg/day) is better tolerated and has greater efficacy than deoxycholate formulation in this setting[11,12,36] and should be considered when initial treatment with other regimens fails **(AII)**.

Higher doses of fluconazole in combination with flucytosine also may be useful **(BIII)**. Echinocandins have no activity against *Cryptococcus* spp. and **are not recommended** for clinical management of cryptococcosis **(AII)**. The newer triazoles—posaconazole and voriconazole—have activity against *Cryptococcus* spp. *in vitro* and may have a role in salvage therapy, but probably offer no specific advantages over fluconazole unless *in vitro* susceptibility testing indicates fluconazole resistance. Most clinical failures are a result of inadequate induction therapy, drug interactions that interfere with treatment, or development of IRIS and are not due to drug resistance.

Preventing Recurrence

When to Start Secondary Prophylaxis

Patients who have completed the first 10 weeks of induction and consolidation therapy for acute cryptococcosis should be given chronic maintenance or suppressive therapy with fluconazole 200 mg daily **(AI)**. Itraconazole is inferior to fluconazole for preventing relapse of cryptococcal disease and **should not be used (CI)**.[23]

When to Stop Secondary Prophylaxis

Only a small number of patients have been evaluated for relapse after successful antifungal therapy for cryptococcosis and discontinuation of secondary prophylaxis while on ART. In a European study, recurrence of cryptococcosis was seen in none of 39 subjects on potent ART whose antifungal therapy was discontinued. In this cohort, when maintenance therapy was stopped, the median CD4 cell count was 297 cells/mm^3, the median HIV RNA concentration was <500 copies/mL, and the median time on potent ART was 25 months.[37] A prospective, randomized study of 60 patients in Thailand documented no recurrences of cryptococcosis during 48 weeks of follow-up among 22 patients whose antifungal therapy was discontinued after having achieved a CD4 count >100 cells/mm^3 with a sustained undetectable HIV RNA level for 3 months on potent ART.[38] Given these data and inference from data on discontinuation of secondary prophylaxis for other HIV-associated opportunistic infections, it is reasonable to discontinue chronic antifungal maintenance therapy for cryptococcosis in patients whose CD4 cell counts are ≥100 cells/mm^3, who have undetectable viral loads on ART for >3 months, and who have received a minimum of 1 year of azole antifungal chronic maintenance therapy after successful treatment of cryptococcosis **(BII)**.[39] Secondary prophylaxis should be reinitiated if the CD4 count decreases again to <100 cells/mm^3 **(AIII)**.

Special Considerations During Pregnancy

The diagnosis of cryptococcal infections during pregnancy is similar to that in non-pregnant adults. Treatment should be initiated promptly after a diagnosis is confirmed. It should be emphasized that the postpartum period may be a high-risk period for the development of IRIS.

Lipid formulations of amphotericin B are the preferred initial regimen for the treatment of cryptococcal meningoencephalitis, disseminated disease, or severe pulmonary cryptococcosis in pregnant patients. Extensive clinical experience with amphotericin has not documented teratogenicity. Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Flucytosine was teratogenic in animal studies, and human experience is limited to case reports and small series. Therefore, its use should be considered only when the benefits outweigh its risks to the fetus **(CIII)**.

Congenital malformations similar to those observed in animals, including craniofacial and limb abnormalities, have been reported in infants born to mothers who received fluconazole at doses of ≥400 mg/day or more through or beyond the first trimester of pregnancy.[40] Although several cohort studies have shown no increased risk of birth defects with early pregnancy exposure, most of these involved low doses and short term exposure to fluconazole.[41,42] Based on the reported birth defects, the FDA has changed the pregnancy category for fluconazole from C to D for any use other than a single, low dose for treatment of vaginal candidiasis, (http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm) and use of fluconazole in the first trimester should be considered only if the benefits clearly outweigh risks. For pregnant women, amphotericin should be continued throughout the first trimester with consideration of switching to oral fluconazole, if clinically appropriate, after the first trimester.

Although there are case reports of birth defects in infants exposed to itraconazole, prospective cohort studies of over 300 women with first trimester exposure did not show an increased risk of malformation.[43,44] However, in general azole antifungals **should be avoided** during the first trimester of pregnancy **(BIII)**. Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies, voriconazole at doses lower than recommended human doses; there are no adequate controlled studies in humans. These drugs **should be avoided** in pregnancy, especially in the first trimester **(AIII)**.

Recommendations for Preventing and Treating Cryptococcosis (page 1 of 2)

Treating Cryptococcal Meningitis

Induction Therapy (For At Least 2 Weeks, Followed by Consolidation Therapy)

Preferred Regimens:
• Liposomal amphotericin B 3–4 mg/kg IV daily + flucytosine 25 mg/kg PO QID **(AI)**

Note: Flucytosine dose should be adjusted in renal impairment

Alternative Regimens:
• Amphotericin B lipid complex 5 mg/kg IV daily + flucytosine 25 mg/kg PO QID **(BII)**
• Amphotericin B (deoxycholate 0.7-1.0 mg/kg IV daily + flucytosine 25 mg/kg PO QID **(AI)**
• Liposomal amphotericin B 3–4 mg/kg IV daily + fluconazole 800 mg PO or IV daily **(BIII)**
• Amphotericin B (deoxycholate 0.7-1.0 mg/kg IV daily) + fluconazole 800 mg PO or IV daily **(BI)**
• Liposomal amphotericin B 3-4 mg/kg IV daily alone **(BII)**
• Fluconazole 400–800 mg PO or IV daily + flucytosine 25 mg/kg PO QID **(BII)**
• Fluconazole 1200 mg PO or IV daily alone **(CII)**

Consolidation Therapy (For At Least 8 Weeks, Followed by Maintenance Therapy)
• To begin after at least 2 weeks of successful induction therapy (defined as substantial clinical improvement and a negative CSF culture after repeat LP)

Preferred Regimen:
• Fluconazole 400 mg PO or IV once daily **(AI)**

Alternative Regimen:
• Itraconazole 200 mg PO BID **(CI)**

Maintenance Therapy

Preferred Regimen:
• Fluconazole 200 mg PO for at least 1 year **(AI)**

Recommendations for Preventing and Treating Cryptococcosis (page 2 of 2)

Stopping Maintenance Therapy

If the following criteria are fulfilled (BII):

- Completed initial (induction, consolidation) therapy, and at least 1 year on maintenance therapy, *and*

- Remains asymptomatic from cryptococcal infection, *and*

- CD4 count ≥100 cells/µL for ≥3 months and suppressed HIV RNA in response to effective ART

Restarting Maintenance Therapy:

- If CD4 count decline to ≤100 cells/µL **(AIII)**

Treating Non-CNS, Extrapulmonary Cryptococcosis and for Diffuse Pulmonary Disease:

- Same treatment as for CNS disease **(BIII)**

Treating Non-CNS Cryptococococcosis with Mild-to-Moderate Symptoms and Focal Pulmonary Infiltrates:

- Fluconazole 400 mg PO daily for 12 months **(BIII)**

Other Considerations

- Addition of flucytosine to amphotericin B has been associated with more rapid sterilization of CSF, decreased risk for subsequent relapse, and improved survival.

- Patients receiving flucytosine should have either blood levels monitored (peak level 2 hours after dose should be between 30–80 µg/mL) or close following of complete blood counts to identify developing cytopenias. Dosage should be adjusted in patients with renal insufficiency **(BII)**.

- Opening pressure should always be measured when a LP is performed. Repeated LPs or CSF shunting are essential to effectively manage symptomatic increased ICP.

- Corticosteroids and mannitol are ineffective in reducing ICP and are NOT recommended **(BII)**.

- Infection due to *C. gattii* should be treated similarly to *C. neoformans* **(BIII)**.

- All the triazole antifungals have the potential to interact with certain antiretroviral agents and other anti-infective agents. These interactions are complex and can be bidirectional. Table 5 lists these interactions and recommends dosage adjustments where feasible.

Key to Acronyms: BID = twice daily; CD4 = CD4 T lymphocyte cell; CNS = central nervous system; CSF = cerebrospinal fluid; ICP = intracranial pressure; IV = intravenous; LP = lumbar puncture; PO = orally; QID = four times a day

References

1. Aberg J, WG. P. Cryptococcosis. In: Dolin R MH, Saag MS, ed. *AIDS Therapy*. New York, NY: Churcill Livingstone; 2002:498-510.

2. Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. *AIDS*. Feb 20 2009;23(4):525-530. Available at http://www.ncbi.nlm.nih.gov/pubmed/19182676.

3. Mirza SA, Phelan M, Rimland D, et al. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992-2000. *Clin Infect Dis*. Mar 15 2003;36(6):789-794. Available at http://www.ncbi.nlm.nih.gov/pubmed/12627365.

4. Graybill JR, Sobel J, Saag M, et al. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. *Clin Infect Dis*. Jan 2000;30(1):47-54. Available at http://www.ncbi.nlm.nih.gov/pubmed/10619732.

5. Bicanic T, Brouwer AE, Meintjes G, et al. Relationship of cerebrospinal fluid pressure, fungal burden and outcome in patients with cryptococcal meningitis undergoing serial lumbar punctures. *AIDS*. Mar 27 2009;23(6):701-706. Available at http://www.ncbi.nlm.nih.gov/pubmed/19279443.

6. French N, Gray K, Watera C, et al. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. *AIDS*. May 3 2002;16(7):1031-1038. Available at http://www.ncbi.nlm.nih.gov/pubmed/11953469.

7. Powderly WG, Cloud GA, Dismukes WE, Saag MS. Measurement of cryptococcal antigen in serum and cerebrospinal fluid: value in the management of AIDS-associated cryptococcal meningitis. *Clin Infect Dis*. May 1994;18(5):789-792.

Available at http://www.ncbi.nlm.nih.gov/pubmed/8075272.

8. Powderly WG, Finkelstein D, Feinberg J, et al. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *N Engl J Med*. Mar 16 1995;332(11):700-705. Available at http://www.ncbi.nlm.nih.gov/pubmed/7854376.

9. McKinsey DS, Wheat LJ, Cloud GA, et al. Itraconazole prophylaxis for fungal infections in patients with advanced human immunodeficiency virus infection: randomized, placebo-controlled, double-blind study. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *Clin Infect Dis*. May 1999;28(5):1049-1056. Available at http://www.ncbi.nlm.nih.gov/pubmed/10452633.

10. Baddour LM, Perfect JR, Ostrosky-Zeichner L. Successful use of amphotericin B lipid complex in the treatment of cryptococcosis. *Clin Infect Dis*. May 1 2005;40 Suppl 6:S409-413. Available at http://www.ncbi.nlm.nih.gov/pubmed/15809927.

11. Leenders AC, Reiss P, Portegies P, et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. *AIDS*. Oct 1997;11(12):1463-1471. Available at http://www.ncbi.nlm.nih.gov/pubmed/9342068.

12. Hamill RJ, Sobel JD, El-Sadr W, et al. Comparison of 2 doses of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis: a randomized, double-blind clinical trial of efficacy and safety. *Clin Infect Dis*. Jul 15 2010;51(2):225-232. Available at http://www.ncbi.nlm.nih.gov/pubmed/20536366.

13. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *N Engl J Med*. Jul 3 1997;337(1):15-21. Available at http://www.ncbi.nlm.nih.gov/pubmed/9203426.

14. Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. *Clin Infect Dis*. Apr 2000;30(4):710-718. Available at http://www.ncbi.nlm.nih.gov/pubmed/10770733.

15. Dromer F, Mathoulin-Pelissier S, Launay O, Lortholary O, French Cryptococcosis Study G. Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. *PLoS Med*. Feb 2007;4(2):e21. Available at http://www.ncbi.nlm.nih.gov/pubmed/17284154.

16. Dromer F, Bernede-Bauduin C, Guillemot D, Lortholary O, French Cryptococcosis Study G. Major role for amphotericin B-flucytosine combination in severe cryptococcosis. *PLoS One*. 2008;3(8):e2870. Available at http://www.ncbi.nlm.nih.gov/pubmed/18682846.

17. Day JN, Chau TT, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. *N Engl J Med*. Apr 4 2013;368(14):1291-1302. Available at http://www.ncbi.nlm.nih.gov/pubmed/23550668.

18. Brouwer AE, Rajanuwong A, Chierakul W, et al. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. *Lancet*. May 29 2004;363(9423):1764-1767. Available at http://www.ncbi.nlm.nih.gov/pubmed/15172774.

19. Pappas PG, Chetchotisakd P, Larsen RA, et al. A phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of HIV-associated cryptococcal meningitis. *Clin Infect Dis*. Jun 15 2009;48(12):1775-1783. Available at http://www.ncbi.nlm.nih.gov/pubmed/19441980.

20. Larsen RA, Bozzette SA, Jones BE, et al. Fluconazole combined with flucytosine for treatment of cryptococcal meningitis in patients with AIDS. *Clin Infect Dis*. Oct 1994;19(4):741-745. Available at http://www.ncbi.nlm.nih.gov/pubmed/7803641.

21. Bicanic T, Meintjes G, Wood R, et al. Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naive or antiretroviral-experienced patients treated with amphotericin B or fluconazole. *Clin Infect Dis*. Jul 1 2007;45(1):76-80. Available at http://www.ncbi.nlm.nih.gov/pubmed/17554704.

22. Nussbaum JC, Jackson A, Namarika D, et al. Combination flucytosine and high-dose fluconazole compared with fluconazole monotherapy for the treatment of cryptococcal meningitis: a randomized trial in Malawi. *Clin Infect Dis*. Feb 1 2010;50(3):338-344. Available at http://www.ncbi.nlm.nih.gov/pubmed/20038244.

23. Saag MS, Cloud GA, Graybill JR, et al. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *Clin Infect Dis*. Feb 1999;28(2):291-296. Available at http://www.ncbi.nlm.nih.gov/pubmed/10064246.

24. Powderly WG, Saag MS, Cloud GA, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. The NIAID AIDS Clinical Trials Group and Mycoses Study Group. *N Engl J Med*. Mar 19 1992;326(12):793-798. Available at http://www.ncbi.nlm.nih.gov/pubmed/1538722.

25. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Infect Dis*. May 1 2003;36(9):1122-1131. Available at http://www.ncbi.nlm.nih.gov/pubmed/12715306.

26. Pitisuttithum P, Negroni R, Graybill JR, et al. Activity of posaconazole in the treatment of central nervous system fungal infections. *J Antimicrob Chemother*. Oct 2005;56(4):745-755. Available at http://www.ncbi.nlm.nih.gov/pubmed/16135526.

27. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4(5):e5575. Available at http://www.ncbi.nlm.nih.gov/pubmed/19440326.

28. Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. *Clin Infect Dis*. Jun 1 2010;50(11):1532-1538. Available at http://www.ncbi.nlm.nih.gov/pubmed/20415574.

29. Fessler RD, Sobel J, Guyot L, et al. Management of elevated intracranial pressure in patients with Cryptococcal meningitis. *J Acquir Immune Defic Syndr Hum Retrovirol*. Feb 1 1998;17(2):137-142. Available at http://www.ncbi.nlm.nih.gov/pubmed/9473014.

30. Shelburne SA, 3rd, Darcourt J, White AC, Jr., et al. The role of immune reconstitution inflammatory syndrome in AIDS-related Cryptococcus neoformans disease in the era of highly active antiretroviral therapy. *Clin Infect Dis*. Apr 1 2005;40(7):1049-1052. Available at http://www.ncbi.nlm.nih.gov/pubmed/15825000.

31. Muller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis*. Apr 2010;10(4):251-261. Available at http://www.ncbi.nlm.nih.gov/pubmed/20334848.

32. Boulware DR, Bonham SC, Meya DB, et al. Paucity of initial cerebrospinal fluid inflammation in cryptococcal meningitis is associated with subsequent immune reconstitution inflammatory syndrome. *J Infect Dis*. Sep 15 2010;202(6):962-970. Available at http://www.ncbi.nlm.nih.gov/pubmed/20677939.

33. Haddow LJ, Colebunders R, Meintjes G, et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. *Lancet Infect Dis*. Nov 2010;10(11):791-802. Available at http://www.ncbi.nlm.nih.gov/pubmed/21029993.

34. Brandt ME, Pfaller MA, Hajjeh RA, et al. Trends in antifungal drug susceptibility of Cryptococcus neoformans isolates in the United States: 1992 to 1994 and 1996 to 1998. *Antimicrob Agents Chemother*. Nov 2001;45(11):3065-3069. Available at http://www.ncbi.nlm.nih.gov/pubmed/11600357.

35. Witt MD, Lewis RJ, Larsen RA, et al. Identification of patients with acute AIDS-associated cryptococcal meningitis who can be effectively treated with fluconazole: the role of antifungal susceptibility testing. *Clin Infect Dis*. Feb 1996;22(2):322-328. Available at http://www.ncbi.nlm.nih.gov/pubmed/8838190.

36. Chen SC, Australasian Society for Infectious Diseases Mycoses Iterest G. Cryptococcosis in Australasia and the treatment of cryptococcal and other fungal infections with liposomal amphotericin B. *J Antimicrob Chemother*. Feb 2002;49 Suppl 1(Suppl 1):57-61. Available at http://www.ncbi.nlm.nih.gov/pubmed/11801583.

37. Kirk O, Reiss P, Uberti-Foppa C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. *Ann Intern Med*. Aug 20 2002;137(4):239-250. Available at http://www.ncbi.nlm.nih.gov/pubmed/12186514.

38. Vibhagool A, Sungkanuparph S, Mootsikapun P, et al. Discontinuation of secondary prophylaxis for cryptococcal meningitis in human immunodeficiency virus-infected patients treated with highly active antiretroviral therapy: a prospective, multicenter, randomized study. *Clin Infect Dis*. May 15 2003;36(10):1329-1331. Available at http://www.ncbi.nlm.nih.gov/pubmed/12746781.

39. Mussini C, Pezzotti P, Miro JM, et al. Discontinuation of maintenance therapy for cryptococcal meningitis in patients with AIDS treated with highly active antiretroviral therapy: an international observational study. *Clin Infect Dis*. Feb 15 2004;38(4):565-571. Available at http://www.ncbi.nlm.nih.gov/pubmed/14765351.

40. Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis*. Feb 1996;22(2):336-340. Available at http://www.ncbi.nlm.nih.gov/pubmed/8838193.

41. Norgaard M, Pedersen L, Gislum M, et al. Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study. *J Antimicrob Chemother*. Jul 2008;62(1):172-176. Available at http://www.ncbi.nlm.nih.gov/pubmed/18400803.

42. Mastroiacovo P, Mazzone T, Botto LD, et al. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. *Am J Obstet Gynecol*. Dec 1996;175(6):1645-1650. Available at http://www.ncbi.nlm.nih.gov/pubmed/8987954.

43. De Santis M, Di Gianantonio E, Cesari E, Ambrosini G, Straface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. *Drug Saf*. 2009;32(3):239-244. Available at http://www.ncbi.nlm.nih.gov/pubmed/19338381.

44. Bar-Oz B, Moretti ME, Bishai R, et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol*. Sep 2000;183(3):617-620. Available at http://www.ncbi.nlm.nih.gov/pubmed/10992182.

Histoplasmosis (Last updated May 7, 2013; last reviewed May 7, 2013)

Epidemiology

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. Infection is endemic to the central and south-central United States and is especially common in the Ohio and Mississippi River Valleys. It is also endemic in Latin America, including Puerto Rico. In endemic areas, annual incidence approaches 5% in HIV-infected individuals. A CD4 T lymphocyte (CD4) count <150 cells/mm^3 is associated with an increased risk of symptomatic illness.[1,2]

Virtually all cases of primary histoplasmosis are acquired by inhalation of microconidia that form in the mycelial phase. Asymptomatic dissemination of infection beyond the lungs is common, and cellular immunity is critical in controlling infection. When cellular immunity wanes, reactivation of a silent focus of infection that was acquired years earlier can occur, and it is the presumed mechanism for disease occurrence in nonendemic areas. Incidence of symptomatic histoplasmosis in HIV-infected patients appears to have declined with the advent of effective antiretroviral therapy (ART). When histoplasmosis does occur, however, it is reported as the AIDS-defining illness in 25% to 61% of patients.[3,4]

Clinical Manifestations

In HIV-infected patients, common clinical manifestations of progressive disseminated histoplasmosis include fever, fatigue, weight loss, and hepatosplenomegaly. Cough, chest pain, and dyspnea occur in approximately 50% of patients.[1,4] Central nervous system (CNS), gastrointestinal, and cutaneous manifestations occur in a smaller percentage, although in a series from Panama, diarrhea occurred in 50% of patients.[5] Approximately 10% of patients experience shock and multi-organ failure. Patients with CNS histoplasmosis typically experience fever and headache, and also (if brain involvement is present) seizures, focal neurological deficits, and changes in mental status.[6] Gastrointestinal disease usually manifests as diarrhea, fever, abdominal pain, and weight loss.[7] For patients whose CD4 counts are >300 cells/mm^3, histoplasmosis is often limited to the respiratory tract and usually presents with cough, pleuritic chest pain, and fever.

Diagnosis

Detection of *Histoplasma* antigen in blood or urine is a sensitive method for rapid diagnosis of disseminated histoplasmosis and acute pulmonary histoplasmosis[8] but is insensitive for chronic forms of pulmonary infection. Using a newer quantitative assay, antigen was detected in the urine of 100% and in the serum of 92% of AIDS patients with disseminated histoplasmosis.[9] Antigen detection in bronchoalveolar lavage fluid appears to be a useful method for diagnosis of pulmonary histoplasmosis.[10] In patients with severe disseminated histoplasmosis, peripheral blood smears can show the organisms engulfed by white blood cells. Histopathological examination of biopsy material from involved tissues demonstrates the characteristic 2 to 4 μm budding yeast and can provide a rapid diagnosis.

H. capsulatum can be cultured from blood, bone marrow, respiratory secretions, or other involved sites in >85% of patients with AIDS and disseminated histoplasmosis, but the organism requires several weeks to grow.[11] Serologic tests are less useful than antigen assays in AIDS patients with disseminated histoplasmosis but may be helpful in patients who have reasonably intact immune responses with pulmonary disease.[11,12]

The diagnosis of meningitis is often difficult. The usual cerebrospinal fluid (CSF) findings are a lymphocytic pleocytosis, elevated protein, and low glucose. Fungal stains are usually negative, and CSF cultures are positive in a minority of cases.[6] However, *Histoplasma* antigen or antibodies against *H. capsulatum* can be detected in CSF in up to 70% of cases, and a positive result for either test is diagnostic. For some patients, none of these specific tests is positive, and a presumptive diagnosis of *Histoplasma* meningitis is appropriate if the patient has disseminated histoplasmosis and findings of CNS infection not explained by another cause.

Preventing Exposure

HIV-infected individuals who live in or visit areas in which histoplasmosis is endemic cannot completely avoid exposure to it, but those with CD4 counts <150 cells/mm^3 should avoid activities known to be associated with increased risk **(BIII)**. These include creating dust when working with surface soil; cleaning chicken coops that are contaminated with droppings; disturbing areas contaminated with bird or bat droppings; cleaning, remodeling, or demolishing old buildings; and exploring caves.

Preventing Disease

When to Start Primary Prophylaxis

Data from a prospective, randomized, controlled trial indicate that itraconazole can reduce the frequency of histoplasmosis, although not mortality, in patients who have advanced HIV infection and who live in areas where histoplasmosis is highly endemic.[13] Prophylaxis with itraconazole at a dose of 200 mg daily can be considered for patients with CD4 counts <150 cells/mm^3 who are at high risk because of occupational exposure or who live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) **(BI)**.

When to Stop Primary Prophylaxis

If used, primary prophylaxis can be discontinued in patients on potent ART once CD4 counts are ≥150 cells/mm^3 for 6 months **(BIII)**. Prophylaxis should be restarted if the CD4 count falls to <150 cells/mm^3 **(BIII)**.

Treating Disease

In a randomized clinical trial, intravenous (IV) liposomal amphotericin B (3 mg/kg daily) was more effective than standard IV amphotericin B deoxycholate (0.7 mg/kg daily), induced a more rapid and complete response, lowered mortality, and reduced toxicity.[14] Based on these findings, patients with moderately severe to severe disseminated histoplasmosis should be treated with IV liposomal amphotericin B (3 mg/kg daily) for at least 2 weeks or until they clinically improve **(AI)**. Another lipid formulation of amphotericin B can be used at the same dosage if cost is a concern or in patients who cannot tolerate liposomal amphotericin B **(AIII)**. Step-down therapy to oral itraconazole, 200 mg 3 times daily for 3 days, and then 200 mg twice daily, should be given for a total of at least 12 months **(AII)**.[15] Because of potential drug interactions between itraconazole and both protease inhibitors and efavirenz, it is advisable to obtain serum levels of itraconazole after 2 weeks of therapy. A randomly obtained serum level of at least 1.0 µg/mL is recommended and levels >10 µg/mL are unnecessary.

In patients with less severe disseminated histoplasmosis, oral itraconazole, 200 mg 3 times daily for 3 days followed by 200 mg twice daily, is appropriate initial therapy **(AII)**.[15,16] The liquid formulation of itraconazole, which should be given on an empty stomach, is preferable because it is better absorbed and does not require gastric acid for absorption, but it is less well tolerated than the capsule formulation, which should be given with food.

Acute pulmonary histoplasmosis in an HIV-infected patient with intact immunity, as indicated by a CD4 count >300 cells/mm^3, should be managed in a manner similar to that used for a nonimmunocompromised host **(AIII)**.[15]

In patients with confirmed meningitis, liposomal amphotericin B should be administered as initial therapy at a dosage of 5 mg/kg daily for 4 to 6 weeks **(AIII)**. This should be followed by maintenance therapy with itraconazole at a dose of 200 mg 2 or 3 times daily for at least 1 year and until resolution of abnormal CSF findings **(AIII)**.[15]

Oral posaconazole and voriconazole have been reported to be effective for histoplasmosis in a small number of patients who had AIDS or other immunosuppressive conditions[17-20] and may be reasonable alternatives for patients intolerant of itraconazole who are only moderately ill **(BIII)**. Fluconazole is less effective than

itraconazole for histoplasmosis but has been shown to be moderately effective at a dose of 800 mg daily and may also be a reasonable alternative at this dose for those intolerant of itraconazole **(CII)**.[21] The echinocandins are not active against *H. capsulatum* and **should not be used** to treat patients with histoplasmosis **(AIII)**.

Special Considerations with Regard to Starting ART

HIV-infected individuals diagnosed with histoplasmosis should be started on ART as soon as possible after initiating antifungal therapy **(AIII)**. Immune reconstitution inflammatory syndrome (IRIS) is reportedly uncommon in HIV-infected patients with histoplasmosis.[22,23] ART should, therefore, **not** be withheld because of concern for the possible development of IRIS **(AIII)**.

All of the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain ARV agents and other anti-infective agents. Table 5 lists these interactions and recommendations for dosage adjustments, where feasible.

Monitoring of Response to Therapy and Adverse Events (including IRIS)

Serial monitoring of serum or urine for *Histoplasma* antigen is useful for determining response to therapy. A rise in antigen level suggests relapse. Because absorption of itraconazole can be erratic, a random serum itraconazole level should be obtained after 2 weeks of therapy if there is concern about adherence or if medications with potentially adverse interactions are added to the drug regimen. The serum concentration should be >1 µg/mL.

As previously indicated, IRIS is uncommon in HIV-infected individuals with histoplasmosis.[22,23]

Managing Treatment Failure

Mortality rates remain high for patients with AIDS who develop disseminated histoplasmosis, many of whom had never received ART before diagnosis with histoplasmosis.[3-5,12] Liposomal amphotericin B should be used in patients who are severely ill or who have failed to respond to initial azole antifungal therapy **(AIII)**. Oral posaconazole and voriconazole are reasonable alternatives for patients intolerant of itraconazole who are only moderately ill **(BIII)**;[17-20] fluconazole also can be used at a dose of 800 mg daily **(CII)**.[21] Drug interactions may limit the use of voriconazole in patients who are taking non-nucleoside reverse transcriptase inhibitors or ritonavir (Table 5). Posaconazole has fewer known drug interactions with ARV medications than voriconazole.

Preventing Recurrence

When to Start Secondary Prophylaxis

Long-term suppressive therapy with itraconazole (200 mg daily) should be administered to patients with severe disseminated or CNS infection **(AIII)** and after re-induction therapy in those whose disease relapses despite initial receipt of appropriate therapy **(BIII)**. Fluconazole is less effective than itraconazole for this purpose but has some efficacy at 400 mg daily.[21,24] The role of voriconazole or posaconazole has not been evaluated.

When to Stop Secondary Prophylaxis

An AIDS Clinical Treatment Group (ACTG)-sponsored study reported that discontinuing itraconazole was safe for patients treated for histoplasmosis who have a good immunologic response to ART.[25] Subjects in that trial had received >1 year of itraconazole therapy; had negative fungal blood cultures, a *Histoplasma* serum antigen <2 units, and CD4 counts ≥150 cells/mm^{3}; and had been on effective ART for 6 months. No relapses were evident in 32 subjects who were followed for a median of 24 months.[25] Thus, discontinuing suppressive azole antifungal therapy appears to be safe for patients who meet the previously described criteria, noting that the detectable antigen level is now designated as 2 ng/mL **(AI)**. Suppressive therapy should be resumed if the CD4 count decreases to <150 cells/mm^{3} **(BIII)**.

Special Considerations During Pregnancy

Amphotericin B or its lipid formulations are the preferred initial regimen for the treatment of histoplasmosis in pregnant patients. Extensive clinical experience with amphotericin has not documented teratogenicity. At delivery, infants born to women treated with amphotericin B should be evaluated for renal dysfunction and hypokalemia. Although there are case reports of birth defects in infants exposed to itraconazole, prospective cohort studies of over 300 women with first trimester exposure did not show an increased risk of malformation.[26,27] However, in general, azole antifungals **should be avoided** during the first trimester of pregnancy **(BIII)**. Congenital malformations similar to those observed in animals, including craniofacial and limb abnormalities, have been reported in infants born to mothers who received fluconazole at doses of 400 mg/day or more through or beyond the first trimester of pregnancy.[28] Although several cohort studies have shown no increased risk of birth defects with early pregnancy exposure, most of these studies involved low doses and short term exposure to fluconazole.[29,30] Based on the reported birth defects, the Food and Drug Administration has changed the pregnancy category from C to D for fluconazole for any use other than a single, low dose for treatment of vaginal candidiasis (http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm). Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies, voriconazole at doses lower than recommended human doses; there are no adequate controlled studies in humans. These drugs **should be avoided** in pregnancy, especially in the first trimester **(AIII)**.

Recommendations for Preventing and Treating *Histoplasma capsulatum* Infections (page 1 of 2)

Preventing 1st Episode of *Histoplasma capsulatum* Infection (Primary Prophylaxis)

Indications for Initiating Primary Prophylaxis:
- CD4 count <150 cells/mm^3 and at high risk because of occupational exposure or living in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) **(BI)**

Preferred Therapy:
- Itraconazole 200 mg PO once daily **(BI)**

Discontinue Primary Prophylaxis:
- If used, may discontinue if CD4 count ≥150 cells/mm^3 for 6 months on ART **(BIII)**

Indication for Restarting Primary Prophylaxis:
- CD4 count <150 cells/mm^3 **(BIII)**

Treating Moderately Severe to Severe Disseminated Disease

Induction Therapy
Preferred Therapy:
- Liposomal amphotericin B at 3 mg/kg IV daily **(AI)**

Alternative Therapy:
- Amphotericin B lipid complex or amphotericin B cholesteryl sulfate complex 3 mg/kg IV daily **(AIII)**

Duration:
- For at least 2 weeks or until clinically improved

Maintenance Therapy
Preferred Therapy:
- Itraconazole 200 mg PO TID for 3 days, then BID for at least 12 months **(AII)**, with dosage adjustment based on interactions with ARV (see Table 5) and itraconazole serum concentration

Treating Less Severe Disseminated Disease

Induction and Maintenance Therapy
Preferred Therapy:
- Itraconazole 200 mg PO TID for 3 days, then 200 mg PO BID for ≥12 months **(AII)**, with dosage adjustment based on interactions with ARV and itraconazole serum concentration

Alternative Therapy:

Note: These recommendations are based on limited clinical data (for patients intolerant to itraconazole who are only moderately ill).

• Posaconazole 400 mg PO BID **(BIII)**

• Voriconazole 400 mg PO BID for 1 day, then 200 mg PO BID **(BIII)**

• Fluconazole 800 mg PO daily **(CII)**

Treating Histoplasma Meningitis

Induction Therapy (4–6 Weeks):

• Liposomal amphotericin B: 5 mg/kg IV daily **(AIII)**

Maintenance Therapy

• Itraconazole 200 mg PO BID (TID for at least 12 months and until resolution of abnormal CSF findings) with dosage adjustment based on interactions with ARV and itraconazole serum concentration **(AIII)**

Long-Term Suppressive Therapy (Secondary Prophylaxis)

Indications:

• For patients with severe disseminated or CNS infection after completion of at least 12 months of treatment **(AIII)**, *and*

• In patients who relapsed despite appropriate initial therapy **(BIII)**

Preferred Therapy:

• Itraconazole 200 mg PO daily **(AIII)**

Alternative Therapy:

• Fluconazole 400 mg PO daily **(BIII)**

*Criteria for Discontinuing Long Term Suppressive Therapy **(AI)**:*

• Received azole treatment for >1 year, *and*

• Negative fungal blood cultures, *and*

• Serum Histoplasma antigen <2 ng/mL, *and*

• CD4 count >150 cells/mm^3 for ≥6 months in response to ART

Indication for Restarting Secondary Prophylaxis:

• CD4 count <150 cells/mm^3 **(BIII)**

Other Considerations:

• Itraconazole serum concentrations should be performed in all patients to ensure adequate absorption and to assess changes in hepatic metabolism due to drug interactions **(AIII)**. Random serum concentrations (itraconazole + hydroxyitraconazole) should be >1 µg/mL.

• Itraconazole oral solution is preferred over capsule because of improved absorption, but is less well tolerated. However, this formulation may not be necessary if itraconazole concentration is increased by concomitant use of a CYP3A4 inhibitor such as ritonavir-boosted PIs.

• Acute pulmonary histoplasmosis in HIV-infected patients with CD4 count >300 cells/mm^3 should be managed the same as for non-immunocompromised patients **(AIII)**

• All the triazole antifungals have the potential to interact with certain ARV agents and other anti-infective agents. These interactions are complex and can be bidirectional. Table 5 lists these interactions and recommends dosage adjustments where feasible.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte cell; CNS = central nervous system, CSF = cerebrospinal fluid; CYP3A4 = Cytochrome P450 3A4; IV = intravenous; PI = protease inhibitor; PO = orally; TID = three times daily

References

1. Wheat LJ, Connolly-Stringfield PA, Baker RL, et al. Disseminated histoplasmosis in the acquired immune deficiency syndrome: clinical findings, diagnosis and treatment, and review of the literature. *Medicine (Baltimore)*. Nov 1990;69(6):361-374. Available at http://www.ncbi.nlm.nih.gov/pubmed/2233233.

2. McKinsey DS, Spiegel RA, Hutwagner L, et al. Prospective study of histoplasmosis in patients infected with human immunodeficiency virus: incidence, risk factors, and pathophysiology. *Clin Infect Dis*. Jun 1997;24(6):1195-1203. Available at http://www.ncbi.nlm.nih.gov/pubmed/9195082.

3. Antinori S, Magni C, Nebuloni M, et al. Histoplasmosis among human immunodeficiency virus-infected people in Europe: report of 4 cases and review of the literature. *Medicine (Baltimore)*. Jan 2006;85(1):22-36. Available at http://www.ncbi.nlm.nih.gov/pubmed/16523050.

4. Baddley JW, Sankara IR, Rodriquez JM, Pappas PG, Many WJ, Jr. Histoplasmosis in HIV-infected patients in a southern regional medical center: poor prognosis in the era of highly active antiretroviral therapy. *Diagn Microbiol Infect Dis*. Oct 2008;62(2):151-156. Available at http://www.ncbi.nlm.nih.gov/pubmed/18597967.

5. Gutierrez ME, Canton A, Sosa N, Puga E, Talavera L. Disseminated histoplasmosis in patients with AIDS in Panama: a review of 104 cases. *Clin Infect Dis*. Apr 15 2005;40(8):1199-1202. Available at http://www.ncbi.nlm.nih.gov/pubmed/15791523.

6. Wheat LJ, Musial CE, Jenny-Avital E. Diagnosis and management of central nervous system histoplasmosis. *Clin Infect Dis*. Mar 15 2005;40(6):844-852. Available at http://www.ncbi.nlm.nih.gov/pubmed/15736018.

7. Assi M, McKinsey DS, Driks MR, et al. Gastrointestinal histoplasmosis in the acquired immunodeficiency syndrome: report of 18 cases and literature review. *Diagn Microbiol Infect Dis*. Jul 2006;55(3):195-201. Available at http://www.ncbi.nlm.nih.gov/pubmed/16545932.

8. Swartzentruber S, Rhodes L, Kurkjian K, et al. Diagnosis of acute pulmonary histoplasmosis by antigen detection. *Clin Infect Dis*. Dec 15 2009;49(12):1878-1882. Available at http://www.ncbi.nlm.nih.gov/pubmed/19911965.

9. Connolly PA, Durkin MM, Lemonte AM, Hackett EJ, Wheat LJ. Detection of histoplasma antigen by a quantitative enzyme immunoassay. *Clin Vaccine Immunol*. Dec 2007;14(12):1587-1591. Available at http://www.ncbi.nlm.nih.gov/pubmed/17913863.

10. Hage CA, Davis TE, Fuller D, et al. Diagnosis of histoplasmosis by antigen detection in BAL fluid. *Chest*. Mar 2010;137(3):623-628. Available at http://www.ncbi.nlm.nih.gov/pubmed/19837826.

11. Wheat LJ. Approach to the diagnosis of the endemic mycoses. *Clin Chest Med*. Jun 2009;30(2):379-389, viii. Available at http://www.ncbi.nlm.nih.gov/pubmed/19375642.

12. Tobon AM, Agudelo CA, Rosero DS, et al. Disseminated histoplasmosis: a comparative study between patients with acquired immunodeficiency syndrome and non-human immunodeficiency virus-infected individuals. *Am J Trop Med Hyg*. Sep 2005;73(3):576-582. Available at http://www.ncbi.nlm.nih.gov/pubmed/16172484.

13. McKinsey DS, Wheat LJ, Cloud GA, et al. Itraconazole prophylaxis for fungal infections in patients with advanced human immunodeficiency virus infection: randomized, placebo-controlled, double-blind study. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *Clin Infect Dis*. May 1999;28(5):1049-1056. Available at http://www.ncbi.nlm.nih.gov/pubmed/10452633.

14. Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. *Ann Intern Med*. Jul 16 2002;137(2):105-109. Available at http://www.ncbi.nlm.nih.gov/pubmed/12118965.

15. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. Oct 1 2007;45(7):807-825. Available at http://www.ncbi.nlm.nih.gov/pubmed/17806045.

16. Wheat J, Hafner R, Korzun AH, et al. Itraconazole treatment of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trial Group. *Am J Med*. Apr 1995;98(4):336-342. Available at http://www.ncbi.nlm.nih.gov/pubmed/7709945.

17. Freifeld AG, Iwen PC, Lesiak BL, Gilroy RK, Stevens RB, Kalil AC. Histoplasmosis in solid organ transplant recipients at a large Midwestern university transplant center. *Transplant infectious disease: an official journal of the Transplantation Society*. Sep-Dec 2005;7(3-4):109-115. Available at http://www.ncbi.nlm.nih.gov/pubmed/16390398.

18. Al-Agha OM, Mooty M, Salarieh A. A 43-year-old woman with acquired immunodeficiency syndrome and fever of undetermined origin. Disseminated histoplasmosis. *Archives of pathology & laboratory medicine*. Jan 2006;130(1):120-123. Available at http://www.ncbi.nlm.nih.gov/pubmed/16390228.

19. Restrepo A, Tobon A, Clark B, et al. Salvage treatment of histoplasmosis with posaconazole. *J Infect*. Apr 2007;54(4):319-327. Available at http://www.ncbi.nlm.nih.gov/pubmed/16824608.

20. Freifeld A, Proia L, Andes D, et al. Voriconazole use for endemic fungal infections. *Antimicrob Agents Chemother*. Apr 2009;53(4):1648-1651. Available at http://www.ncbi.nlm.nih.gov/pubmed/19139290.

21. Wheat J, MaWhinney S, Hafner R, et al. Treatment of histoplasmosis with fluconazole in patients with acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Acquired Immunodeficiency Syndrome Clinical Trials Group and Mycoses Study Group. *Am J Med*. Sep 1997;103(3):223-232. Available at http://www.ncbi.nlm.nih.gov/pubmed/9316555.

22. Shelburne SA, 3rd, Darcourt J, White AC, Jr., et al. The role of immune reconstitution inflammatory syndrome in AIDS-related Cryptococcus neoformans disease in the era of highly active antiretroviral therapy. *Clin Infect Dis*. Apr 1 2005;40(7):1049-1052. Available at http://www.ncbi.nlm.nih.gov/pubmed/15825000.

23. Nacher M, Sarazin F, El Guedj M, et al. Increased incidence of disseminated histoplasmosis following highly active antiretroviral therapy initiation. *J Acquir Immune Defic Syndr*. Apr 1 2006;41(4):468-470. Available at http://www.ncbi.nlm.nih.gov/pubmed/16652055.

24. Hecht FM, Wheat J, Korzun AH, et al. Itraconazole maintenance treatment for histoplasmosis in AIDS: a prospective, multicenter trial. *J Acquir Immune Defic Syndr Hum Retrovirol*. Oct 1 1997;16(2):100-107. Available at http://www.ncbi.nlm.nih.gov/pubmed/9358104.

25. Goldman M, Zackin R, Fichtenbaum CJ, et al. Safety of discontinuation of maintenance therapy for disseminated histoplasmosis after immunologic response to antiretroviral therapy. *Clin Infect Dis*. May 15 2004;38(10):1485-1489. Available at http://www.ncbi.nlm.nih.gov/pubmed/15156489.

26. De Santis M, Di Gianantonio E, Cesari E, Ambrosini G, Straface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. *Drug Saf*. 2009;32(3):239-244. Available at http://www.ncbi.nlm.nih.gov/pubmed/19338381.

27. Bar-Oz B, Moretti ME, Bishai R, et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol*. Sep 2000;183(3):617-620. Available at http://www.ncbi.nlm.nih.gov/pubmed/10992182.

28. Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis*. Feb 1996;22(2):336-340. Available at http://www.ncbi.nlm.nih.gov/pubmed/8838193.

29. Norgaard M, Pedersen L, Gislum M, et al. Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study. *J Antimicrob Chemother*. Jul 2008;62(1):172-176. Available at http://www.ncbi.nlm.nih.gov/pubmed/18400803.

30. Mastroiacovo P, Mazzone T, Botto LD, et al. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. *Am J Obstet Gynecol*. Dec 1996;175(6):1645-1650. Available at http://www.ncbi.nlm.nih.gov/pubmed/8987954.

Coccidioidomycosis (Last updated May 7, 2013; last reviewed May 7, 2013)

Epidemiology

Coccidioidomycosis is caused by a soil-dwelling fungus that consists of two species, *Coccidioides immitis* and *Coccidioides posadasii*. Most cases of coccidioidomycosis in HIV-infected individuals have been reported in the areas in which the disease is highly endemic.[1] In the United States, these areas include the lower San Joaquin Valley in California; much of Arizona; the southern regions of Utah, Nevada, and New Mexico; and western Texas.[2] Cases have been diagnosed outside those areas, presumably as a result of reactivation of an infection previously acquired in an endemic region.

Risk of developing symptomatic disease is increased in HIV-infected patients living in an endemic area who have CD4 T lymphocyte (CD4) cell counts <250 cells/mm^3 or who have been diagnosed with AIDS.[3] Incidence and severity of HIV-associated coccidioidomycosis have declined since the introduction of effective antiretroviral therapy (ART).[4,5]

Clinical Manifestations

Lack of suppression of HIV replication and lower CD4 cell counts are significantly associated with the severity of the presentation of coccidioidomycosis.[5] Six common syndromes of coccidioidomycosis have been described in HIV-infected patients: focal pneumonia, diffuse pneumonia, cutaneous disease, meningitis, liver or lymph node involvement, and positive coccidioidal serology tests without evidence of localized infection.[6]

Focal pneumonia is most common in patients with CD4 counts ≥250 cells/mm^3. This diagnosis can be difficult to distinguish from a bacterial community-acquired pneumonia; patients present with symptoms that include cough, fever, and pleuritic chest pain.[7,8] The other syndromes usually occur in more immunosuppressed patients. Diffuse pulmonary disease presents with fever and dyspnea and can be difficult to clinically distinguish from *Pneumocystis* pneumonia.[9] Meningitis presents with a persistent headache and progressive lethargy. The cerebrospinal fluid (CSF) profile demonstrates a low glucose level with elevated protein and a lymphocytic pleocytosis.

Diagnosis

The diagnosis of coccidioidomycosis is confirmed by culture of the organism from clinical specimens or by demonstration of the typical spherule on histopathological examination of involved tissue. Blood cultures are positive in a minority of patients, usually those with diffuse pulmonary disease. Coccidioidal immunoglobulin M (IgM) and immunoglobulin G (IgG) serology, performed by enzyme immunoassay, immunodiffusion, or classical tube precipitin or complement fixation methodology, is useful in diagnosis but may be positive less often in patients with low CD4 cell counts than in those who are immunocompetent.[10] Complement fixation IgG antibody often is detected in the CSF in coccidioidal meningitis and is useful in establishing this diagnosis. Culture of the CSF is positive in less than one-third of patients with meningitis. A coccidioidomycosis-specific antigen assay recently has become commercially available. It has been shown to detect antigen in urine[11] and serum[12] samples from HIV-infected individuals with active coccidioidomycosis and appears to be useful in diagnosing coccidioidomycosis in such patients.

Preventing Exposure

HIV-infected individuals cannot completely avoid activities involving exposure to infection while living in or visiting areas in which *Coccidioides* spp. are endemic. They should, however, avoid extensive exposure to disturbed native soil, such as at building excavation sites, and stay inside during dust storms **(BIII)**.

Preventing Disease

Primary antifungal prophylaxis is of little benefit to patients with low CD4 cell counts who live in regions where *Coccidioides* spp. are endemic[4] and it **is not recommended (AIII)**.

Yearly serologic testing for coccidioidomycosis is reasonable for HIV-infected individuals who live in regions endemic for coccidioidomycosis. In such settings, a new positive test suggests imminent active disease in patients with low CD4 cell counts[13] and pre-emptive antifungal therapy with fluconazole 400 mg daily is recommended for those with CD4 counts <250/mm^3 **(BIII)**. Outside endemic regions, routine testing does not appear to be useful and should not be performed.

Treating Disease

Initial therapy with a triazole antifungal is appropriate for patients who have clinically mild infection, such as focal pneumonia **(BII)**. Fluconazole or itraconazole at doses of 400 mg daily is recommended.[14,15] Data are limited on the newer triazoles (posaconazole[16,17] and voriconazole), but these agents may be useful for patients who fail to respond to fluconazole or itraconazole.

Amphotericin B is the preferred initial therapy for patients who have diffuse pulmonary involvement or are severely ill with extrathoracic disseminated disease **(AII)**.[15] Most experience has been with the deoxycholate formulation, using an initial dose of 0.7 to 1.0 mg/kg intravenously (IV) daily. No data exist about use of lipid formulations of amphotericin B, but they are likely to be as effective as the deoxycholate formulation and may be considered as an alternative initial therapy **(AIII)**.

Therapy with amphotericin B should continue until clinical improvement is observed. Some specialists recommend combining amphotericin B with a triazole (either fluconazole or itraconazole, with itraconazole preferred for bone disease) at 400 mg daily at initiation of therapy, and then continue the triazole once amphotericin B is stopped **(BIII)**.[15]

Treatment of patients with coccidioidal meningitis requires consultation with a specialist. Therapy should begin with a triazole antifungal. IV or oral fluconazole at a dose of 400 to 800 mg daily is preferred **(AII)**,[18] but itraconazole also has been used successfully **(BII)**.[19] Successful therapy with posaconazole **(CIII)**[17,20] and voriconazole **(BIII)**[21-23] has been described in individual cases. Despite successful antifungal therapy, some patients may develop hydrocephalus and require CSF shunting. In some instances, triazole antifungals are ineffective and intrathecal amphotericin B is recommended **(AIII)**. Intrathecal amphotericin B should be administered by someone with experience in this technique.

Special Considerations with Regard to Starting ART

HIV-infected individuals diagnosed with coccidioidomycosis should be started on ART as soon as possible after initiating antifungal therapy **(AIII)**. Immune reconstitution inflammatory syndrome (IRIS) has been reported once[24] but concern for the syndrome should not delay initiation of ART **(AIII)**.

Monitoring of Response to Therapy and Adverse Events (including IRIS)

Monitoring the titer of the complement-fixing antibody is useful in assessing response to therapy, and it should be measured every 12 weeks. A rise suggests recurrence or worsening of clinical disease and should prompt reassessment of management. As indicated in previous sections, all of the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain ARV agents and other anti-infective agents. Table 5 lists such interactions and recommendations for dosage adjustments, where feasible.

Managing Treatment Failure

Patients with severe coccidioidomycosis who fail treatment with fluconazole or itraconazole should have their treatment changed to IV amphotericin B, either deoxycholate or lipid formulation **(AIII)**. For patients who are not severely ill, posaconazole **(BII)** and voriconazole **(BIII)**—both given in doses of 200 mg orally twice

daily—can be considered, although data are limited regarding their efficacy. Drug interactions may limit the use of voriconazole in patients who are taking non-nucleoside reverse transcriptase inhibitors or ritonavir (see Table 5). Posaconazole has fewer known drug interactions with ARV medications than does voriconazole.

Preventing Recurrence

When To Start Secondary Prophylaxis

Patients who complete initial therapy for coccidioidomycosis should be considered for lifelong suppressive therapy using either fluconazole 400 mg daily or itraconazole 200 mg twice daily if their CD4 counts remain <250 cells/mm^{3} **(AII)**. Posaconazole 200 mg twice daily **(BII)** or voriconazole 200 mg twice daily **(BIII)** are alternatives if the patient did not initially respond to either fluconazole or itraconazole.

When To Stop Secondary Prophylaxis

Patients with focal coccidioidal pneumonia who have clinically responded to antifungal therapy appear to be at low risk of recurrence of coccidioidomycosis if their CD4 cell counts are ≥250 cells/mm^{3} and they are receiving effective ART. A reasonable plan for treating these individuals is to discontinue secondary prophylaxis after 12 months of therapy **(AII)** and continue monitoring for recurrence with serial chest radiographs and coccidioidal serology.

Relapse occurs in 25% to 33% of HIV-uninfected patients who have diffuse pulmonary disease or nonmeningeal disseminated coccidioidomycosis[25,26] and can occur in HIV-infected patients with CD4 counts ≥250 cells/mm^{3} on potent ART;[27] therefore, some clinicians would continue antifungal therapy indefinitely **(BIII)**, although this decision should be made in conjunction with expert consultation. Because relapses have been reported in 80% of patients with meningitis in whom triazoles have been discontinued,[28] therapy for coccidioidal meningitis should be lifelong **(AII)**.

Special Considerations During Pregnancy

Coccidioidomycosis is more likely to disseminate if acquired during the second or third trimester of pregnancy.[29] Amphotericin B or its lipid formulations are the preferred initial regimen for the treatment of coccidioidomycosis in pregnant patients. Extensive clinical use of amphotericin has not been associated with teratogenicity. At delivery, infants born to women treated with amphotericin B should be evaluated for renal dysfunction and hypokalemia.

Congenital malformations similar to those observed in animals, including craniofacial and limb abnormalities, have been reported in infants born to mothers who received fluconazole through or beyond the first trimester of pregnancy.[30] Although several cohort studies have shown no increased risk of birth defects with early pregnancy exposure to fluconazole, most of these involved low doses and short term exposure.[31,32] Based on the reported birth defects, the Food and Drug Administration has changed the pregnancy category from C to D for fluconazole for any use other than a single, 150 mg dose to treat vaginal candidiasis (http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm). Although there are case reports of birth defects in infants exposed to itraconazole, prospective cohort studies of over 300 women with first trimester exposure did not show an increased risk of malformation.[33,34] However, in general, azole antifungals **should be avoided** during the first trimester of pregnancy **(BIII)**. One problematic area is coccidioidal meningitis, in which the only alternative treatment to triazole antifungals is intrathecal amphotericin B. For such situations, the decision regarding choice of treatment should be based on considerations of benefit versus potential risk and made in consultation with the mother, the infectious diseases consultant, and the obstetrician.[35] Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies, voriconazole at doses lower than recommended human doses; there are no adequate controlled studies in humans. These drugs **should be avoided** in pregnancy, especially in the first trimester **(AIII)**.

Primary Prophylaxis

Indication:

• A new positive IgM or IgG serologic test in patients who live in a disease-endemic area and with CD4 counts <250 cells/µL **(BIII)**

Regimen:

• Fluconazole 400 mg PO once daily **(BIII)**

Treating Mild Infections (Such As Focal Pneumonia)

Preferred Therapy:

• Fluconazole 400 mg PO once daily **(BII)**, *or*

• Itraconazole 200 mg PO twice daily **(BII)**

Alternative Therapy (For Patients Who Failed To Respond To Fluconazole Or Itraconazole):

• Posaconazole 200–400 mg PO twice daily **(BII)**; *or*

• Voriconazole 200 mg PO twice daily **(BIII)**

Treating Severe, Non-Meningeal Infection (Diffuse Pulmonary or Severely Ill Patients with Extrathoracic Disseminated Disease)—Acute Phase

Preferred Therapy:

• Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily **(AII)**, *or*

• Lipid formulation amphotericin B 4–6 mg/kg IV daily **(AIII)**

Duration:

• Until clinical improvement, then switch to triazole **(BIII)**

Alternative Therapy:

• Some specialists add a triazole (either fluconazole or itraconazole, with itraconazole preferred for bone disease) at 400 mg daily to amphotericin B therapy and continue triazole once amphotericin B is stopped **(BIII)**

Treatment For Meningeal Infections (Consultation With A Specialist Is Advised)

Preferred Therapy:

• Fluconazole 400–800 mg IV or PO daily **(AII)**

Alternative Therapy:

• Itraconazole 200 mg PO twice daily **(BII)**, *or*

• Posaconazole 200–400 mg PO twice daily **(CIII)**, *or*

• Voriconazole 200–400 mg PO twice daily **(BIII)**, *or*

• Intrathecal amphotericin B **(AIII)** when triazole antifungals are not effective. Use in consultation with a specialist and should be administered by someone with experience in this technique.

Chronic Suppressive Therapy

Preferred Therapy:

• Fluconazole 400 mg PO daily **(AII)**, *or*

• Itraconazole 200 mg PO twice daily **(AII)**

Alternative Therapy (If Patients Did Not Initially Respond to Fluconazole or Itraconazole):

• Posaconazole 200 mg PO twice daily **(BII)**, *or*

• Voriconazole 200 mg PO twice daily **(BIII)**

Discontinuing Chronic Suppressive Therapy

Focal Coccidioidal Pneumonia, Suppressive Therapy Can Be Stopped If **(AII)**:

• Clinically responded to >12 months of antifungal therapy, *and*

• CD4 count ≥250 cells/mm^3, *and*

• Receiving effective ART, *and*

• Continued monitoring for recurrence using serial chest radiograph and coccidioidal serology.

Diffuse Pulmonary Disease or Non-Meningeal Disseminated Coccidioidomycosis:

• Relapse can occur in 25% to 33% of HIV-negative patients, and can occur in HIV patients with CD4 count >250 cells/mm^3

• Some clinicians would continue therapy indefinitely; this decision should be made in consultation with experts **(BIII)**.

Coccidioidal Meningitis:

• Relapse has been reported in 80% of patients after stopping triazoles, therefore, suppressive therapy should be lifelong **(AII)**

Other Considerations:

• Certain patients with meningitis may develop hydrocephalus and require CSF shunting in addition to antifungal therapy.

• All the triazole antifungals have the potential to interact with certain antiretroviral agents and other anti-infective agents. These interactions are complex and can be bidirectional. Table 5 lists these interactions and recommends dosage adjustments where feasible.

Key to Acronyms: CD4 = CD4 T lymphocyte cell; CSF = cerebrospinal fluid; IgG = immunogloblulin G; IgM = immunoglobulin M; IV = intravenous; PO = orally

References

1. Jones JL, Fleming PL, Ciesielski CA, Hu DJ, Kaplan JE, Ward JW. Coccidioidomycosis among persons with AIDS in the United States. *J Infect Dis*. Apr 1995;171(4):961-966. Available at http://www.ncbi.nlm.nih.gov/pubmed/7706825.

2. Centers for Disease C, Prevention. Increase in Coccidioidomycosis - California, 2000-2007. *MMWR Morb Mortal Wkly Rep*. Feb 13 2009;58(5):105-109. Available at http://www.ncbi.nlm.nih.gov/pubmed/19214158.

3. Ampel NM, Dols CL, Galgiani JN. Coccidioidomycosis during human immunodeficiency virus infection: results of a prospective study in a coccidioidal endemic area. *Am J Med*. Mar 1993;94(3):235-240. Available at http://www.ncbi.nlm.nih.gov/pubmed/8095771.

4. Woods CW, McRill C, Plikaytis BD, et al. Coccidioidomycosis in human immunodeficiency virus-infected persons in Arizona, 1994-1997: incidence, risk factors, and prevention. *J Infect Dis*. Apr 2000;181(4):1428-1434. Available at http://www.ncbi.nlm.nih.gov/pubmed/10753734.

5. Masannat FY, Ampel NM. Coccidioidomycosis in patients with HIV-1 infection in the era of potent antiretroviral therapy. *Clin Infect Dis*. Jan 1 2010;50(1):1-7. Available at http://www.ncbi.nlm.nih.gov/pubmed/19995218.

6. Fish DG, Ampel NM, Galgiani JN, et al. Coccidioidomycosis during human immunodeficiency virus infection. A review of 77 patients. *Medicine (Baltimore)*. Nov 1990;69(6):384-391. Available at http://www.ncbi.nlm.nih.gov/pubmed/2146461.

7. Valdivia L, Nix D, Wright M, et al. Coccidioidomycosis as a common cause of community-acquired pneumonia. *Emerg Infect Dis*. Jun 2006;12(6):958-962. Available at http://www.ncbi.nlm.nih.gov/pubmed/16707052.

8. Kim MM, Blair JE, Carey EJ, Wu Q, Smilack JD. Coccidioidal pneumonia, Phoenix, Arizona, USA, 2000-2004. *Emerg Infect Dis*. Mar 2009;15(3):397-401. Available at http://www.ncbi.nlm.nih.gov/pubmed/19239751.

9. Mahaffey KW, Hippenmeyer CL, Mandel R, Ampel NM. Unrecognized coccidioidomycosis complicating Pneumocystis carinii pneumonia in patients infected with the human immunodeficiency virus and treated with corticosteroids. A report of two cases. *Arch Intern Med*. Jun 28 1993;153(12):1496-1498. Available at http://www.ncbi.nlm.nih.gov/pubmed/8512440.

10. Singh VR, Smith DK, Lawerence J, et al. Coccidioidomycosis in patients infected with human immunodeficiency virus: review of 91 cases at a single institution. *Clin Infect Dis*. Sep 1996;23(3):563-568. Available at

http://www.ncbi.nlm.nih.gov/pubmed/8879781.

11. Durkin M, Connolly P, Kuberski T, et al. Diagnosis of coccidioidomycosis with use of the Coccidioides antigen enzyme immunoassay. *Clin Infect Dis*. Oct 15 2008;47(8):e69-73. Available at http://www.ncbi.nlm.nih.gov/pubmed/18781884.

12. Durkin M, Estok L, Hospenthal D, et al. Detection of Coccidioides antigenemia following dissociation of immune complexes. *Clin Vaccine Immunol*. Oct 2009;16(10):1453-1456. Available at http://www.ncbi.nlm.nih.gov/pubmed/19675225.

13. Arguinchona HL, Ampel NM, Dols CL, Galgiani JN, Mohler MJ, Fish DG. Persistent coccidioidal seropositivity without clinical evidence of active coccidioidomycosis in patients infected with human immunodeficiency virus. *Clin Infect Dis*. May 1995;20(5):1281-1285. Available at http://www.ncbi.nlm.nih.gov/pubmed/7620011.

14. Galgiani JN, Ampel NM, Catanzaro A, Johnson RH, Stevens DA, Williams PL. Practice guideline for the treatment of coccidioidomycosis. Infectious Diseases Society of America. *Clin Infect Dis*. Apr 2000;30(4):658-661. Available at http://www.ncbi.nlm.nih.gov/pubmed/10770727.

15. Galgiani JN, Ampel NM, Blair JE, et al. Coccidioidomycosis. *Clin Infect Dis*. Nov 1 2005;41(9):1217-1223. Available at http://www.ncbi.nlm.nih.gov/pubmed/16206093.

16. Anstead GM, Corcoran G, Lewis J, Berg D, Graybill JR. Refractory coccidioidomycosis treated with posaconazole. *Clin Infect Dis*. Jun 15 2005;40(12):1770-1776. Available at http://www.ncbi.nlm.nih.gov/pubmed/15909265.

17. Stevens DA, Rendon A, Gaona-Flores V, et al. Posaconazole therapy for chronic refractory coccidioidomycosis. *Chest*. Sep 2007;132(3):952-958. Available at http://www.ncbi.nlm.nih.gov/pubmed/17573510.

18. Galgiani JN, Catanzaro A, Cloud GA, et al. Fluconazole therapy for coccidioidal meningitis. The NIAID-Mycoses Study Group. *Ann Intern Med*. Jul 1 1993;119(1):28-35. Available at http://www.ncbi.nlm.nih.gov/pubmed/8498760.

19. Tucker RM, Denning DW, Dupont B, Stevens DA. Itraconazole therapy for chronic coccidioidal meningitis. *Ann Intern Med*. Jan 15 1990;112(2):108-112. Available at http://www.ncbi.nlm.nih.gov/pubmed/2153012.

20. Schein R, Homans J, Larsen RA, Neely M. Posaconazole for chronic refractory coccidioidal meningitis. *Clin Infect Dis*. Dec 2011;53(12):1252-1254. Available at http://www.ncbi.nlm.nih.gov/pubmed/21987729.

21. Cortez KJ, Walsh TJ, Bennett JE. Successful treatment of coccidioidal meningitis with voriconazole. *Clin Infect Dis*. Jun 15 2003;36(12):1619-1622. Available at http://www.ncbi.nlm.nih.gov/pubmed/12802765.

22. Proia LA, Tenorio AR. Successful use of voriconazole for treatment of Coccidioides meningitis. *Antimicrob Agents Chemother*. Jun 2004;48(6):2341. Available at http://www.ncbi.nlm.nih.gov/pubmed/15155250.

23. Freifeld A, Proia L, Andes D, et al. Voriconazole use for endemic fungal infections. *Antimicrob Agents Chemother*. Apr 2009;53(4):1648-1651. Available at http://www.ncbi.nlm.nih.gov/pubmed/19139290.

24. Mortimer RB, Libke R, Eghbalieh B, Bilello JF. Immune reconstitution inflammatory syndrome presenting as superior vena cava syndrome secondary to Coccidioides lymphadenopathy in an HIV-infected patient. *J Int Assoc Physicians AIDS Care (Chic)*. Nov-Dec 2008;7(6):283-285. Available at http://www.ncbi.nlm.nih.gov/pubmed/18948432.

25. Graybill JR, Stevens DA, Galgiani JN, Dismukes WE, Cloud GA. Itraconazole treatment of coccidioidomycosis. NAIAD Mycoses Study Group. *Am J Med*. Sep 1990;89(3):282-290. Available at http://www.ncbi.nlm.nih.gov/pubmed/2168126.

26. Catanzaro A, Galgiani JN, Levine BE, et al. Fluconazole in the treatment of chronic pulmonary and nonmeningeal disseminated coccidioidomycosis. NIAID Mycoses Study Group. *Am J Med*. Mar 1995;98(3):249-256. Available at http://www.ncbi.nlm.nih.gov/pubmed/7872341.

27. Mathew G, Smedema M, Wheat LJ, Goldman M. Relapse of coccidioidomycosis despite immune reconstitution after fluconazole secondary prophylaxis in a patient with AIDS. *Mycoses*. Feb 2003;46(1-2):42-44. Available at http://www.ncbi.nlm.nih.gov/pubmed/12588482.

28. Dewsnup DH, Galgiani JN, Graybill JR, et al. Is it ever safe to stop azole therapy for Coccidioides immitis meningitis? *Ann Intern Med*. Feb 1 1996;124(3):305-310. Available at http://www.ncbi.nlm.nih.gov/pubmed/8554225.

29. Peterson CM, Schuppert K, Kelly PC, Pappagianis D. Coccidioidomycosis and pregnancy. *Obstetrical & gynecological survey*. Mar 1993;48(3):149-156. Available at http://www.ncbi.nlm.nih.gov/pubmed/8441516.

30. Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis*. Feb 1996;22(2):336-340. Available at http://www.ncbi.nlm.nih.gov/pubmed/8838193.

31. Norgaard M, Pedersen L, Gislum M, et al. Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study. *J Antimicrob Chemother*. Jul 2008;62(1):172-176. Available at http://www.ncbi.nlm.nih.gov/pubmed/18400803.

32. Mastroiacovo P, Mazzone T, Botto LD, et al. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. *Am J Obstet Gynecol*. Dec 1996;175(6):1645-1650. Available at http://www.ncbi.nlm.nih.gov/pubmed/8987954.

33. De Santis M, Di Gianantonio E, Cesari E, Ambrosini G, Straface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. *Drug Saf*. 2009;32(3):239-244. Available at http://www.ncbi.nlm.nih.gov/pubmed/19338381.

34. Bar-Oz B, Moretti ME, Bishai R, et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol*. Sep 2000;183(3):617-620. Available at http://www.ncbi.nlm.nih.gov/pubmed/10992182.

35. Bercovitch RS, Catanzaro A, Schwartz BS, Pappagianis D, Watts DH, Ampel NM. Coccidioidomycosis during pregnancy: a review and recommendations for management. *Clin Infect Dis*. Aug 2011;53(4):363-368. Available at http://www.ncbi.nlm.nih.gov/pubmed/21810749.

Aspergillosis (Last updated May 7, 2013; last reviewed May 7, 2013)

Epidemiology

Invasive aspergillosis is rare in HIV-infected individuals but often overlooked antemortem. In a recent autopsy series of HIV-infected patients from Italy, invasive aspergillosis was the second most frequently identified invasive mycosis in fatal cases, 88% of which were diagnosed only postmortem.[1] Illness most often is caused by *Aspergillus fumigatus*, but *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreu*s have been noted to cause disease. Invasive aspergillosis occurs in patients with advanced HIV infection and was more common before the advent of effective antiretroviral therapy (ART).[1-3] Specific risk factors include neutropenia, use of corticosteroids, exposure to broad-spectrum antibacterial therapy, and underlying lung disease. Patients who have had HIV-associated aspergillosis typically have CD4 T lymphocyte (CD4) cell counts <100 cells/mm^3, a history of other AIDS-defining opportunistic infections, and are not receiving potent ART.[4]

Clinical Manifestations

In HIV-infected patients, invasive aspergillosis most commonly presents as a respiratory illness that can be a necrotizing pneumonia or a tracheobronchitis.[5] Symptoms of pneumonia include fever, cough, dyspnea, chest pain, hemoptysis, and hypoxemia; chest radiograph may demonstrate a diffuse, focal, or cavitary infiltrate. A halo of low attenuation surrounding a pulmonary nodule or a cavity on a computed tomography (CT) scan of the lung is suggestive of pulmonary aspergillosis. Tracheobronchitis is associated with fever, cough, dyspnea, stridor, and wheezing. Bronchoscopic examination demonstrates ulcerative or plaque-like lesions adherent to the tracheal wall.[6] Extrapulmonary forms of invasive aspergillosis include sinusitis, cutaneous disease, osteomyelitis, and brain abscess.[7]

Diagnosis

The diagnosis of probable invasive pulmonary aspergillosis is based on isolation of *Aspergillus* spp. from respiratory secretions or the finding of septate hyphae consistent with *Aspergillus* spp. in respiratory samples in association with typical CT findings. Histological evidence of tissue invasion by septate hyphae with a positive culture for *Aspergillus* spp. establishes a definitive diagnosis.[8]

Detection of *Aspergillus* cell wall galactomannan by enzyme-linked immunosorbent assay (ELISA) performed on serum or bronchoalveolar lavage fluid has not been formally evaluated in HIV-infected patients. It has proven useful, however, in other immunosuppressed patients, especially recipients of stem cell transplants,[9] and is listed by the European Organisation for Research and Treatment of Cancer/U.S. Mycosis Study Group Consensus Group as one of the criteria for establishing a diagnosis of probable invasive aspergillosis.[8] Bronchoalveolar lavage galactomannan is probably more sensitive than serum galactomannan for diagnosis. The test is highly specific.

Preventing Exposure

Aspergillus spp. are ubiquitous in the environment, and exposure is unavoidable. Avoiding particularly dusty environments, especially areas of construction, is prudent because spore counts likely are higher in such settings.

Preventing Disease

No data exist about the prevention of primary aspergillosis in HIV-infected patients, although posaconazole has been reported to be effective in patients with certain hematological malignancies and neutropenia.[10] At this time, antifungal therapy **is not recommended** for prevention of aspergillosis in HIV-infected individuals **(AIII)**.

Treating Disease

Treatment of aspergillosis in HIV-infected patients has not been systematically examined. Voriconazole is the

recommended treatment for invasive aspergillosis in HIV-uninfected patients **(AI)**.[11] Because of drug-drug interactions, however, voriconazole should be used cautiously with protease inhibitors (PIs) and efavirenz (see Table 5). Alternatively, lipid-formulation amphotericin B or amphotericin B deoxycholate can be used **(AII)**. Second-line agents include echinocandins (such as caspofungin, anidulafungin, or micafungin) or posaconazole **(BIII)**. The role of combination antifungal therapy for primary treatment of invasive aspergillosis is being evaluated in a large, randomized trial comparing voriconazole alone with voriconazole plus anidulafungin in recipients of stem cell transplants. The length of therapy has not been established, but treatment should continue at least until the peripheral blood CD4 count is >200 cells/mm³ and the infection appears to be resolved **(BIII)**.

Special Considerations with Regard to Starting ART

HIV-infected individuals diagnosed with aspergillosis should be started on ART as soon as possible after initiating antifungal therapy **(AIII)**. Immune reconstitution inflammatory syndrome (IRIS) has rarely been reported in HIV-infected patients with invasive aspergillosis[12] and concern for the syndrome should not delay initiation of ART **(AIII)**.

All of the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain antiretroviral agents and other anti-infective agents. Table 5 lists such interactions and recommendations for dosage adjustments, where feasible.

Monitoring of Response to Therapy and Adverse Events (including IRIS)

Data are limited with regard to monitoring of *Aspergillus* galactomannan levels in response to therapy. As previously stated, IRIS rarely has been reported in HIV-infected patients with invasive aspergillosis[12] and new or recurrent signs and symptoms should prompt evaluation for relapse or recurrence of aspergillosis.

Managing Treatment Failure

The overall prognosis for invasive aspergillosis is poor in patients with advanced immunosuppression and in the absence of effective ART. No data are available to guide recommendations for management of treatment failure. If voriconazole was used initially, substitution can be considered with an amphotericin B formulation or with echinocandins in combination with voriconazole or amphotericin B **(BIII)**.

Preventing Recurrence

No data are available on which to base a recommendation for or against chronic maintenance or suppressive therapy in patients who have successfully completed an initial course of treatment.

Special Considerations During Pregnancy

Amphotericin B or its lipid formulations are the preferred initial regimen for the treatment of aspergillosis in pregnant patients. Extensive clinical experience with amphotericin has not documented teratogenicity. At delivery, infants born to women treated with amphotericin B should be evaluated for renal dysfunction and hypokalemia.

Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies, voriconazole at doses lower than recommended human doses; here are no adequate controlled studies in humans. These drugs **should generally be avoided** in pregnancy, especially in the first trimester **(AIII)**. The echinocandins are associated with bony and visceral abnormalities in animal studies, but no human experience is documented. These agents should be avoided in the first trimester of pregnancy; use in later pregnancy should be based on consideration of benefit versus potential risk.

Recommendations for Treating Invasive Aspergillosis

> **Treating Invasive Aspergillosis**
>
> *Preferred Therapy:*
>
> • Voriconazole[a] 6 mg/kg IV q12h for 1 day, then 4 mg/kg IV q12h , followed by voriconazole PO 200 mg q12h after clinical improvement **(AI)**
>
> *Alternative Therapy:*
>
> • Lipid formulation amphotericin B 5 mg/kg/day IV **(AII)**, *or*
>
> • Amphotericin B deoxycholate 1 mg/kg/day IV **(AII)**, *or*
>
> • Caspofungin 70 mg IV once, then 50 mg IV daily **(BIII)**, *or*
>
> • Micafungin 100–150 mg IV daily **(BIII)**, or
>
> • Anidulafungin 200 mg IV once, then 100 mg IV daily **(BIII)**, *or*
>
> • Posaconazole 200 mg QID PO, then 400 mg BID PO after condition improved **(BIII)**
>
> *Duration **(BIII)**:*
>
> • Until CD4 count >200 cells/mm^3 and infection appears to be resolved.

[a] Potential for significant pharmacokinetic interactions between protease inhibitors or non-nucleoside reverse transciptase inhibitors with voriconazole (see Table 5); this agent should be used cautiously in these situations. Therapeutic drug monitoring and dosage adjustment, if necessary, should be performed when using voriconazole.

Key to Acronyms: BID = twice daily; IV = intravenous; PO = orally; Q(n)h = every "n" hours; QID = four times a day

References

1. Antinori S, Nebuloni M, Magni C, et al. Trends in the postmortem diagnosis of opportunistic invasive fungal infections in patients with AIDS: a retrospective study of 1,630 autopsies performed between 1984 and 2002. *Am J Clin Pathol*. Aug 2009;132(2):221-227. Available at http://www.ncbi.nlm.nih.gov/pubmed/19605816.

2. Mylonakis E, Barlam TF, Flanigan T, Rich JD. Pulmonary aspergillosis and invasive disease in AIDS: review of 342 cases. *Chest*. Jul 1998;114(1):251-262. Available at http://www.ncbi.nlm.nih.gov/pubmed/9674477.

3. Holding KJ, Dworkin MS, Wan PC, et al. Aspergillosis among people infected with human immunodeficiency virus: incidence and survival. Adult and Adolescent Spectrum of HIV Disease Project. *Clin Infect Dis*. Nov 2000;31(5):1253-1257. Available at http://www.ncbi.nlm.nih.gov/pubmed/11073760.

4. Wallace JM, Lim R, Browdy BL, et al. Risk factors and outcomes associated with identification of Aspergillus in respiratory specimens from persons with HIV disease. Pulmonary Complications of HIV Infection Study Group. *Chest*. Jul 1998;114(1):131-137. Available at http://www.ncbi.nlm.nih.gov/pubmed/9674459.

5. Lortholary O, Meyohas MC, Dupont B, et al. Invasive aspergillosis in patients with acquired immunodeficiency syndrome: report of 33 cases. French Cooperative Study Group on Aspergillosis in AIDS. *Am J Med*. Aug 1993;95(2):177-187. Available at http://www.ncbi.nlm.nih.gov/pubmed/8395142.

6. Kemper CA, Hostetler JS, Follansbee SE, et al. Ulcerative and plaque-like tracheobronchitis due to infection with Aspergillus in patients with AIDS. *Clin Infect Dis*. Sep 1993;17(3):344-352. Available at http://www.ncbi.nlm.nih.gov/pubmed/8218674.

7. Mylonakis E, Paliou M, Sax PE, Skolnik PR, Baron MJ, Rich JD. Central nervous system aspergillosis in patients with human immunodeficiency virus infection. Report of 6 cases and review. *Medicine (Baltimore)*. Jul 2000;79(4):269-280. Available at http://www.ncbi.nlm.nih.gov/pubmed/10941356.

8. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. Jun 15 2008;46(12):1813-1821. Available at http://www.ncbi.nlm.nih.gov/pubmed/18462102.

9. Maertens JA, Klont R, Masson C, et al. Optimization of the cutoff value for the Aspergillus double-sandwich enzyme immunoassay. *Clin Infect Dis*. May 15 2007;44(10):1329-1336. Available at

http://www.ncbi.nlm.nih.gov/pubmed/17443470.

10. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. Jan 25 2007;356(4):348-359. Available at http://www.ncbi.nlm.nih.gov/pubmed/17251531.

11. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. Feb 1 2008;46(3):327-360. Available at http://www.ncbi.nlm.nih.gov/pubmed/18177225.

12. Sambatakou H, Denning DW. Invasive pulmonary aspergillosis transformed into fatal mucous impaction by immune reconstitution in an AIDS patient. *Eur J Clin Microbiol Infect Dis*. Sep 2005;24(9):628-633. Available at http://www.ncbi.nlm.nih.gov/pubmed/16177885.